REMARKS

Upon entry of the amendments made herein, claims 1, 5-6, 11, 14, 18, 21, 24 and 27 are pending in the application. Claims 2, 8, 12-13, 17, 22-23 and 25-26 have been cancelled herein. Support for new claim 27 can be found at least at page 6, lines 1-5. As requested, Applicants have amended the specification to reflect the relationship between the priority document and this application. No new matter has been added.

I. Rejection under 35 U.S.C. § 112

The claims 1, 2, 5, 6, 8, 11-14, 17, 18, and 21-25 were rejected as failing to comply with the enablement requirement.

The Examiner stated that the claims are directed to methods of delivering a DNA to a spermatogonium of a chicken and the only purpose for the method disclosed in the specification is to make transgenic chicken. (*See*, Office Action page 3). The Examiner also cites the research of Afanassieff et al (Avian Dis. 40:841-852, 1996), Li et al (Transg. Res. 4:26-29, 1995), Ebara (Asian J. Androl. 1(3):139-144, 1999), and Sugihara et al (Comp. Biochem. Phys. B 125:47-52, 200) as further supporting that, at the time the invention was filed, no bird expressing a transgene had been produced by methods in which nucleic acids were delivered to progenitors of sperm cells, regardless of the age of the bird at the time the transgene was introduced. (*See*, Office Action pages 4-5). As such, the Examiner states that the field of making transgenic birds by genetic modification of spermatogonia is considered to be immature and highly unpredictable and with the absence of working examples, one or ordinary skill in the art could not produce transgenic chickens without undue experimentation. (*See*, Office Action page 5). Applicant traverses.

Applicants submit that at the time of the invention gene therapy/*in situ* gene transfer was a well established field of research and is the true basis of the claimed invention. The problems associated with the production of transgenic chickens is, to a large part, inherent in the reproductive physiology of birds, the method of gene transfer and the cells targeted by researchers for gene insertion. The currently claimed invention overcomes these problems by targeting the spermatogonia of the male testicles, which is functionally identical to that of other species, at a time to facilitate gene integration. Applicants contend that the references cited by

the Examiner are not a good basis for comparison to the present invention because of significant differences in the techniques employed or chicken cell targeted.

More specifically, the report by Afanassieff et al. indicates that the studies involved a replication competent virus and the data in no way confirmed actual integration of the virus into the chicken genome only the establishment of an infection. (*See*, Afanassieff et al. at page 845, column 2, first full paragraph). Applicants note that a host immune system is specifically designed to mount a response to an infection by foreign bodies so the elimination of the virus from the testes was to be expected. In addition, retroviral infections will only result in the virus becoming dormant and integrating in the host genome in a small percentage of cases, therefore, the lack of detectable virus in the semen or sperm was also to be predictable. This conclusion is supported by the lack of detectable virus following delivery of the RAV-1 to the blood stream. (*See*, Afanassieff et al. at page 845, column 2, first full paragraph, lines 16-18).

In the case of Li et al. and Ebara et al., the transgene is being delivered to primordial germ cells of the germinal crescent which resulted in the successful production of transgenic chickens that had a high tendency to lose the transgene or stop expression.. (*See*, Li et al., abstract; and Ebara et al., at page 141, column 2, last paragraph). These results validate and support enablement of the claimed invention because they demonstrate the feasibility of producing transgenic chickens. Furthermore, the loss of transgene can most likely be attributed to the choice of primordial germ cell as the target cell. Primordial germ cells represent a unique population of slow dividing migratory cells that makes them a poor choice for gene targeting. Numerous reports in the literature cite the difficulties associated with delivering a transgene to these cells and resultant loss of the transgene during development, which is most probable due to the slow rate of cell division preventing integration. (*See*, Li et al., abstract, last sentence). The invention solves this problem by targeting a different cell type.

The presently pending application describes the delivery of transgene to the rapidly dividing, non-migratory spermatogonia of the testes, thus overcoming many of the inefficiencies associated with Li et al. and Ebara et al. Results are described in the Declaration of Paul A. DiTullio, filed 10/5/06, in which the claimed invention was employed to successfully deliver a transgene to the spermatogonia of roosters which resulted in the production of transgenic spermatogonia and sperm. The definitive fluorescent in situ hybridization technique was used to prove integration of the transgene since an integrated gene appears as a distinct fluorescent spot

as oppose to the dispersed fluorescence of un-integrated DNA. Furthermore, as shown in table 1, column 2 of the Declaration, the presently claimed invention was successfully employed in targeting roosters from 2 to 6 months of age.

Finally, Applicants do not believe that the Sugihara et al reference is relevant to the presently claimed invention since it deals strictly with expression of a transfected gene in a chicken testis rather than production of transgenic sperm. With regard to the persistence of a transgene, Ebara et al. state that even though expression of the transgene is eventually lost, the presence of the transgene was detected, thereby confirming that the chickens were still transgenic. (*See*, Ebara et al. at page 143, column 1, second paragraph).

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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